Stereotactic Body Radiotherapy Using a Radiobiology-Based Regimen for Stage I Non–Small-Cell Lung Cancer

Five-Year Mature Results

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Introduction: Although the protocol of 48 Gy in four fractions over 4 days has been most often employed in stereotactic body radiotherapy (SBRT) for stage I non–small-cell lung cancer in Japan, higher doses are necessary to control larger tumors, and interfraction intervals should be longer than 24 hours to take advantage of reoxygenation. We report the final results of our study testing the following regimen: for tumors less than 1.5, 1.5–3, and greater than 3 cm in diameter, 44, 48, and 52 Gy, respectively, were given in four fractions with interfraction intervals of greater than or equal to 3 days.

Methods: Among 180 histologically proven patients entered, 120 were medically inoperable and 60 were operable. The median patient age was 77 years (range, 29–89). SBRT was performed with 6-MV photons using four noncoplanar and three coplanar beams. Isocenter doses of 44, 48, and 52 Gy were given to four, 124, and 52 patients, respectively.

Results: The 5-year overall survival rate was 52.2% for all 180 patients and 66% for 60 operable patients. The 5-year local control rate was 86% for tumors less than or equal to 3 cm (44/48 Gy) and 73% for tumors greater than 3 cm (52 Gy; $p = 0.076$). Grade greater than or equal to 2 radiation pneumonitis developed in 13% (10% for the 44/48-Gy group and 21% for the 52-Gy group; $p = 0.056$). Other grade 2 toxicities were all less than 4%.

Conclusions: Our first prospective SBRT study yielded reasonable local control and overall survival rates and acceptable toxicity. Refinement of the protocol including dose escalation may lead to better outcome.

Key Words: Lung cancer, Stereotactic body radiotherapy, Stage I, Dose, Fractionation, Reoxygenation.

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Stereotactic body radiotherapy (SBRT) is now the first choice of treatment for medically inoperable patients with stage I non–small-cell lung cancer (NSCLC) and operable patients who refuse surgery.[1–3] Recently reported results suggest that SBRT and surgery yield nearly equivalent outcome.[4–7] Owing to the relatively short history, however, the vast majority of previously published data of SBRT, including those in very recent publications, are middle-term 3-year data.[3,7–10] To compare the two modalities, however, longer-term results, at least 5-year data, are necessary.

In our previous publication, we reported 3-year results of a prospective SBRT study involving three institutions for histologically confirmed stage I NSCLC.[11] Total doses were 44–52 Gy in four fractions; larger tumors were treated with higher doses, and interfraction intervals of at least 72 hours were adopted to efficiently utilize the reoxygenation phenomenon. The rationale for this protocol was discussed in detail previously.[11] Nearly 6 years have passed since the last patient was treated with this protocol, so we analyzed the long-term results.

PATIENTS AND METHODS

Eligibility Criteria and Patients

Approval was obtained from the institutional review boards and informed consent was obtained from all patients. Eligibility criteria were: (1) histologically confirmed stage I NSCLC diagnosed by chest and upper abdomen computed tomography (CT), brain MRI, and bone scintigraphy or fluorodeoxyglucose positron emission tomography (FDG-PET); (2) greatest tumor diameter less than or equal to 5 cm; (3) World Health Organization performance status less than or equal to two or performance status three when its cause was not a pulmonary disease; (4) no prior therapy and no concurrent malignancy; and (5) arterial oxygen pressure greater than or equal to 60 mmHg and forced expiratory volume in 1 second greater than or equal to 700 ml.

Between May 2004 and November 2008, 180 eligible patients entered the study. All completed the planned treatment. Patients were deemed medically inoperable when they had a poor pulmonary function (the ratio of forced expiratory volume in 1 second to forced vital capacity less than 60% and/

or the percent vital capacity less than 75%) or other debilitating conditions that preclude surgery. The patient and tumor characteristics are shown in Table 1. Ages ranged from 29 to 89 years, with a median of 77 years. The longest tumor diameter ranged from 12 to 50 mm, with a median of 27 mm. The tumor location was classified into central or peripheral according to the Radiation Therapy Oncology Group criteria.

Treatment and Evaluation

Our treatment methods were previously described.[11,12] The visible gross tumor volume on CT during three phases (under normal breathing, and with breath holding during the expiratory and inspiratory phases) was superimposed to represent the internal target volume (ITV). The planning target volume (PTV) margin for the ITV was 5 mm in the lateral and anteroposterior directions and 10 mm in the craniocaudal direction.

SBRT was delivered with four fractions using static three coplanar and four noncoplanar 6-MV photon beams. In principle, respective fractions were delivered at intervals of greater than or equal to 72 hours, but owing to national holidays, patient schedule convenience, and machine availability, the actual overall treatment period was 9–21 days (median, 12 days); in 92% of the patients, it was 10–14 days. The total dose at the isocenter was 44 Gy for tumors with a maximum diameter less than 1.5 cm, 48 Gy for tumors of 1.5–3 cm, and 52 Gy for those greater than 3 cm. The dose calculation algorithm was pencil beam convolution with Batho power law correction. It was recommended to cover 95% of the PTV with at least 90% of the isocenter dose, and, in all cases, 95% of the PTV received at least 80% of the prescribed dose. Consequently, 95% of the ITV was covered with greater than or equal to 94% of the prescribed dose in all but one case. Dose constraints for normal tissues were: (1) volume of the lung receiving 20 Gy, less than or equal to 20%; (2) 40 Gy for less than 1 cc of the pulmonary artery and esophagus; (3) 36 Gy for less than 10 cc of the stomach; and (4) maximum cord dose less than 18 Gy. Central and peripheral lesions were treated in the same way.

Chest and upper abdominal CT was performed at 2-month interval until 6 months, and every 2–4 months thereafter. FDG-PET was performed whenever necessary. Local recurrence was diagnosed by serial CT examinations combined with FDG-PET and/or biopsy (two patients). Pleuritis carcinomatosa unaccompanied by local recurrence was regarded as distant metastasis. Toxicity was evaluated using the Common Terminology Criteria for Adverse Events version 3. Follow-up after 5 years was conducted at the discretion of the attending radiation oncologist.

Statistical Analysis

For survival and failure-free rate analyses, the Kaplan–Meier method (from SBRT start) and log-rank test were employed. To evaluate isolated lymph node (regional) failure, patients were censored when they developed local recurrence or pulmonary metastasis. To evaluate isolated distant metastasis, patients were censored when they developed local and/or regional recurrence. The local status was followed until death and patients were not censored even when they developed regional or distant metastasis. Multivariate analysis of potential prognostic factors was carried out using the Cox proportional hazards model. In doing multivariate analysis, patients were divided into two groups and all the parameters were entered as dichotomous variables. Incidences of adverse events were compared using Fisher's exact and χ^2 tests. Statistical softwares used were StatView version 5.0 (SAS Institute, Cary, NC) and HALWIN (Gendaisuugakusha, Kyoto, Japan).

RESULTS

Efficacy

The median follow-up period was 52.5 months for all patients and 72.5 months for living patients. Only one patient

TABLE 1. Patient and Tumor Characteristics

		Stage IA		Stage IB
Characteristic	**All**	**44 Gy**	**48 Gy**	**52 Gy**
Maximum tumor diameter (cm)	1.2–5.0	<1.5	1.5–3	>3
Patient number	180	4	124	52
Age (years)				
Range (median)	29–89 (77)	67–81 (74)	55–87 (77)	29–89 (78)
Sex				
Men/women	123/57	2/2	79/45	42/10
Performance status				
0/1/2/3	87/69/21/3	3/0/1/0	63/47/13/1	21/22/7/2
Operability				
Operable/inoperable	60/120	2/2	43/81	15/37
Histology				
Adeno/squamous/NSCLC	104/60/16	4/0/0	74/37/13	26/23/3
Tumor location				
Center/periphery	35/145	0/4	23/101	12/40

Adeno, adenocarcinoma; squamous, squamous cell carcinoma; NSCLC, unclassified non–small-cell lung cancer.

was lost to follow-up within 3 years. Fifty-five died of the disease, whereas 39 died of intercurrent disease or committed suicide. Overall and cause-specific survival curves and local, regional, and distant metastasis control curves for all patients are shown in Figure 1. For all patients, overall survival rate was 52.2%, cause-specific survival rate was 68.0% and local control rate was 82.6% at 5 years. The regional and distant metastasis control rates at 5 years were 83.8% and 76.3%, respectively.

Figure 2 shows overall survival and local control curves according to the tumor size and prescribed dose. No patients treated with 44 Gy developed local recurrence. The 5-year local control rate was 86% for 124 patients receiving 48 Gy and 73% for those receiving 52 Gy. Figure 3 shows overall survival and local control curves according to operability. The 5-year overall survival was 66% for 60 operable patients and 45% for 120 inoperable patients. The rate was 73% for 45 operable patients with a T1 tumor and 47% for 15 operable patients with a T2 tumor. Survival and control data according to potential prognostic factors are summarized in Table 2.

Toxicities

Grade greater than or equal to 2 radiation pneumonitis was observed in 24 of the 180 patients (13.3%); grade 3 was seen in only two patients (1.1%). Grade greater than or equal to 2 pneumonitis was seen in 13 of 128 patients (10.2%) with a T1 tumor and 11 of 52 patients (21%) with a T2 tumor ($p = 0.056$ by Fisher exact test and 0.049 by χ^2 test). Grade greater than or equal to 2 pneumonitis was seen in 8 of 35 patients (23%) with a central lesion and 16 of 145 patients (11.0%) with a peripheral lesion ($p = 0.11$ by Fisher exact test and 0.096 by χ^2 test). Five of the former eight patients and six of the latter 16 patients had received 52 Gy. Grade 2 or higher esophagitis, rib fracture, and dermatitis were observed in three (1.7%), four (2.2%), and

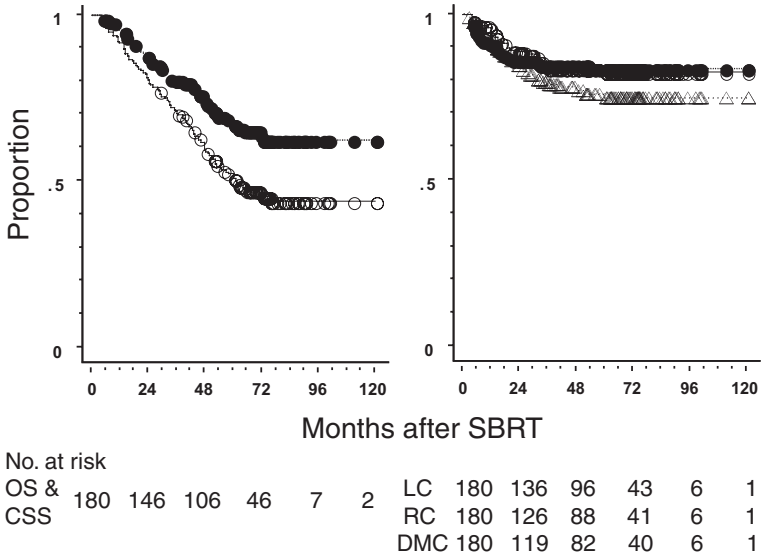

FIGURE 1. *Left panel* OS (*open circle*) and CSS (*filled circle*) curves for all 180 patients. *Right panel* LC (*open circle*), RC (*filled circle*), and DMC (*open triangle*) curves for all 180 patients. OS, overall survival; CSS, cause-specific survival; LC, local control; RC, regional control; DMC, distant metastasis control.

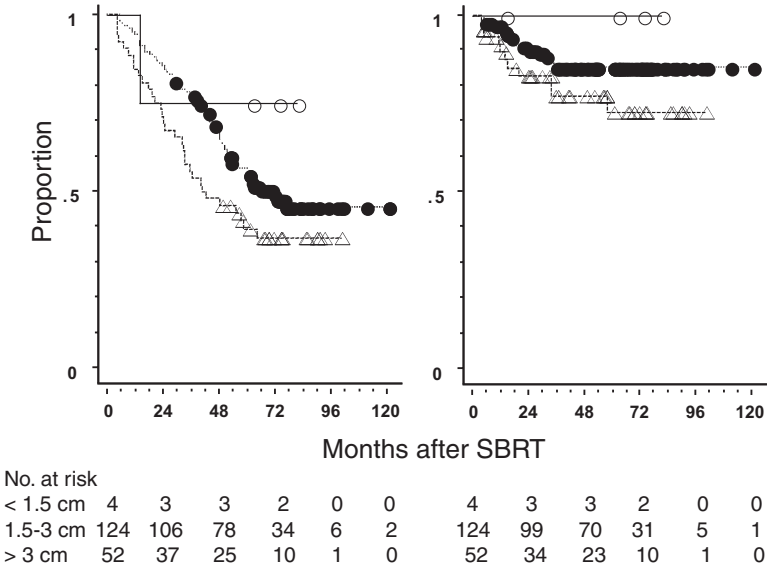

FIGURE 2. Overall survival (*left panel*) and local control (*right panel*) curves according to the tumor size and prescribed dose. *Open circle* Less than 1.5 cm in longest diameter, 44 Gy; *filled circle* 1.5–3 cm, 48 Gy, *open triangle* greater than 3 cm, 52 Gy. 48 Gy versus 52 Gy: $p = 0.043$ for overall survival and 0.092 for local control.

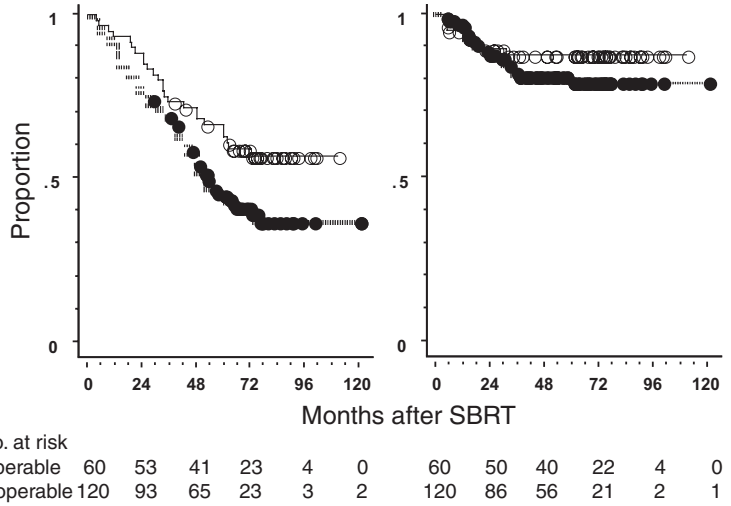

FIGURE 3. Overall survival (*left panel*) and local control (*right panel*) curves for operable (*open circle*) and inoperable (*filled circle*) patients ($p = 0.028$ and 0.31, respectively).

TABLE 2. Five-Year Data According to Patient and Tumor Characteristics

		Overall Survival		Cause-Specific Survival		Local Control		Regional Control		Distant Metastasis Control	
Characteristic	***n***	**%**	***P* (Uni/Multi) Hazard Ratio**	**%**	***P* (Uni/Multi) Hazard Ratio**	**%**	***P* (Uni/Multi) Hazard Ratio**	**%**	***P* (Uni/Multi) Hazard Ratio**	**%**	***P* (Uni/Multi) Hazard Ratio**
Age (years)											
≤79	115	59	0.095/0.079	75	0.062/0.055	83	0.85/0.76	84	0.96/0.89	81	0.22/0.27
≥80	65	40	0.68 (0.44–1.05)	55	0.58 (0.33–1.01)	81	0.89 (0.40–1.96)	85	0.94 (0.39–2.25)	68	0.68 (0.35–1.35)
Sex											
Men	123	46	0.0086/0.073	63	0.016/0.10	79	0.050/0.24	80	0.031/0.10	74	0.25/0.48
Women	57	67	1.65 (0.95–2.86)	79	1.85 (0.88–3.87)	90	1.85 (0.66–5.21)	93	2.90 (0.82–10.3)	81	1.34 (0.59–3.03)
T-stage											
T1	128	57	0.035/0.042	73	0.021/0.016	86	0.076/0.15	87	0.063/0.051	79	0.17/0.16
T2	52	40	0.63 (0.40–0.98)	56	0.49 (0.28–0.87)	73	0.56 (0.25–1.22)	75	0.43 (0.19–1.01)	69	0.60 (0.30–1.22)
Operability											
Operable	60	66	0.028/0.18	74	0.31/0.60	88	0.31/0.70	87	0.40/0.51	79	0.50/0.64
Inoperable	120	45	0.71 (0.43–1.17)	64	0.85 (0.45–1.59)	79	0.84 (0.35–2.03)	82	0.72 (0.26–1.96)	75	0.84 (0.39–1.78)
Histology											
Adeno	104	57	0.025/0.20	72	0.049/0.27	85	0.078/0.31	86	0.51/0.89	76	0.54/0.74
Squamous	60	43	0.74 (0.46–1.18)	60	0.71 (0.39–1.31)	75	0.65 (0.28–1.50)	83	1.07 (0.43–2.62)	76	0.88 (0.42–1.86)
Location											
Center	35	53	0.98/0.62	66	0.91/0.66	79	0.49/0.78	76	0.45/0.63	78	0.50/0.41
Periphery	145	52	0.87 (0.51–1.48)	68	0.85 (0.43–1.72)	84	1.14 (0.46–2.80)	86	1.27 (0.48–3.37)	75	0.68 (0.27–1.69)

Figures in parentheses indicate 95% confidence intervals.
Uni, univariate; Multi, multivariate; Adeno, adenocarcinoma; Squamous, squamous cell carcinoma.

seven of the 180 patients (3.9%), respectively; all patients with grade greater than or equal to 2 rib fracture or dermatitis had a peripheral lesion, whereas two of the three patients with grade 2 esophagitis had a central lesion. Grade 3 pleural effusion and grade 2 cardiac effusion were seen in one patient with a peripheral lesion and one with a central lesion, respectively (0.6%).

DISCUSSION

For medically inoperable patients, the 5-year survival rate of 45% is a marked improvement over conventional radiotherapy, and further discussion on the role of SBRT in this patient population may be unnecessary. On the other hand, SBRT and surgery need to be more deliberately compared in operable NSCLC patients. Randomized trials were attempted, but sufficient patient accrual was not achieved.[7] Because of the marked difference in treatment, randomized comparison may not be easy, so evaluation of long-term results is the only way to discuss this issue at present. Our mature data indicated 5-year survival of 66%, cause-specific survival of 74%, and local control of 88%. These rates may be nearly comparable

to or slightly lower than those reported previously for surgery in clinical stage I NSCLC. Median age of the 60 operable patients was 77 years; the high age might have contributed to the slightly lower survival rate. The study reported here is our first one, and after this study, we escalated the total dose, considering the acceptable toxicities in the 44- and 48-Gy groups. We now use 48 Gy for tumors with a maximum diameter less than 1.5 cm, 50 Gy for tumors of 1.5–3 cm, and 52 Gy in combination with oral S-1 for those greater than 3 cm. The results of the newer study will be published in future; a preliminary analysis suggests slightly improved results (Miyakawa et al., unpublished data, August 2014). Therefore, we would conclude that SBRT is a quite efficient alternative to surgery for patients who do not wish to undergo surgery.

The local control rate of 86% at 5 years for T1 tumors is not too poor, but that for T2 tumors (73%) may be improved in future. One way is to use different fractionation schedules. We are proposing six to eight fraction SBRT for T2 tumors. By employing larger numbers of fractions, normal tissue damage can be suppressed, whereas effects against tumor are expected to increase owing to better utilization of the reoxygenation phenomenon. In previous studies using three different murine tumors, reoxygenation was not complete within 24 hours after 13–15 Gy irradiation, and reoxygenation seemed to proceed further until 72 hours after irradiation.[13] Therefore, we use the twice-weekly schedule for SBRT. Further dose escalation may be feasible and useful especially for T2 tumors by employing a greater number of beams, IMRT, or particle therapy.[14,15]

In conclusion, we reported long-term results of our first prospective SBRT study. The obtained results appear reasonable, but the results may be improved by employing higher doses, larger fraction numbers, and/or particle therapy. Such treatment would be a reasonable alternative to surgery for patients who do not wish to undergo surgery.

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REFERENCES

1. Guckenberger M. Stereotactic body radiotherapy for stage I NSCLC: The challenge of evidence-based medicine. *J Thorac Oncol* 2014;9:e17–e18.
2. Peguret N, Dahele M, Lagerwaard F, Senan S, Slotman BJ. A brief report of 10-year trends in the use of stereotactic lung radiotherapy at a Dutch academic medical center. *J Thorac Oncol* 2014;9:114–117.
3. Nagata Y. Stereotactic body radiotherapy for early stage lung cancer. *Cancer Res Treat* 2013;45:155–161.
4. Onishi H, Shirato H, Nagata Y, et al. Stereotactic body radiotherapy (SBRT) for operable stage I non-small-cell lung cancer: Can SBRT be comparable to surgery? *Int J Radiat Oncol Biol Phys* 2011;81:1352–1358.
5. Varlotto J, Fakiris A, Flickinger J, et al. Matched-pair and propensity score comparisons of outcomes of patients with clinical stage I non-small cell lung cancer treated with resection or stereotactic radiosurgery. *Cancer* 2013;119:2683–2691.
6. Robinson CG, DeWees TA, El Naqa IM, et al. Patterns of failure after stereotactic body radiation therapy or lobar resection for clinical stage I non-small-cell lung cancer. *J Thorac Oncol* 2013;8:192–201.
7. Zheng X, Schipper M, Kidwell K, et al. Survival outcome after stereotactic body radiation therapy and surgery for stage I non-small cell lung cancer: A meta-analysis. *Int J Radiat Oncol Biol Phys* 2014;90:603–611.
8. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA* 2010;303:1070–1076.
9. Takeda A, Sanuki N, Eriguchi T, et al. Stereotactic ablative body radiation therapy for octogenarians with non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2013;86:257–263.
10. Chang JY, Li QQ, Xu QY, et al. Stereotactic ablative radiation therapy for centrally located early stage or isolated parenchymal recurrences of non-small cell lung cancer: How to fly in a "no fly zone". *Int J Radiat Oncol Biol Phys* 2014;88:1120–1128.
11. Shibamoto Y, Hashizume C, Baba F, et al. Stereotactic body radiotherapy using a radiobiology-based regimen for stage I nonsmall cell lung cancer. A multicenter study. *Cancer* 118: 2078–2084, 2012
12. Baba F, Shibamoto Y, Tomita N, et al. Stereotactic body radiotherapy for stage I lung cancer and small lung metastasis: Evaluation of an immobilization system for suppression of respiratory tumor movement and preliminary results. *Radiat Oncol* 2009;4:15.
13. Murata R, Shibamoto Y, Sasai K, et al. Reoxygenation after single irradiation in rodent tumors of different types and sizes. *Int J Radiat Oncol Biol Phys* 1996;34:859–865.
14. Iwata H, Murakami M, Demizu Y, et al. High-dose proton therapy and carbon-ion therapy for stage I nonsmall cell lung cancer. *Cancer* 2010;116:2476–2485.
15. Shibamoto Y. Particle therapy: A suitable alternative to stereotactic body radiotherapy for stage I non-small-cell lung cancer? *Lung Cancer Manage* 2013;2:353–356.